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HAZARD ASSESSMENT OF PERFLUOROOCTANOIC ACID AND ITS SALTS

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PREFACE

This is a preliminary assessment of the potential hazards to human health and the environment associated with exposure to perfluorooctanoic acid (PFOA) and its salts. The majority of the toxicology information is for ammonium perfluorooctanoic acid (APFO). This assessment includes a review of the studies that were available as of July 2001.

A two-generation reproductive toxicity study of APFO is currently being conducted and will be available in the spring of 2002. Effects were observed in a two-generation reproductive toxicity study of a related compound, perfluorooctane sulfonate. The results of the APFO study will be important to determine whether similar effects are observed.

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EXECUTIVE SUMMARY

Introduction

Perfluorooctanoic acid (PFOA) and its salts are fully fluorinated organic compounds that can be produced synthetically or through the degradation or metabolism of other fluorochemical products. PFOA is primarily used as a reactive intermediate, while its salts are used as processing aids in the production of fluoropolymers and fluoroelastomers and in other surfactant uses. In recent years, less than 600 metric tons per year of PFOA and its salts have been manufactured in the United States or imported. Most of the toxicology studies have been conducted with the ammonium salt of perfluorooctanoic acid, which is referred to as APFO in this report.

Environmental Fate and Effects

PFOA is persistent in the environment. It has very low volatility and vapor pressure. It does not hydrolyze, photolyze or biodegrade under environmental conditions.

Several wildlife species have been sampled around the world to determine levels of PFOA. PFOA has rarely been found in fish sampled from the U.S., certain European countries, the North Pacific Ocean and Antarctic locations, or in fish-eating bird samples collected from the U.S., including Midway atoll, the Baltic and Mediterranean Seas, and Japanese and Korean coasts. PFOA was found in a few mink livers from Massachusetts at a concentration range of <18 to 108 ng/g, dry wt., but not found in mink from Louisiana, South Carolina and Illinois. PFOA concentrations in river otter livers from Washington and Oregon States were less than the quantification limit of 36 ng/g, wet wt. PFOA was not detected at quantifiable concentrations in oysters collected in the Chesapeake Bay and Gulf of Mexico of the U.S. coast.

The concentrations of PFOA in surface water, sediments, clams, and fish collected from two locations upstream and five locations downstream of the 3M manufacturing facility at Decatur AL have been determined. Of the five downstream sampling locations, the two closest to the facility had PFOA surface water concentrations significantly greater than the two upstream sites (means of 1900ug/L and 1024 ug/L); the nearest three locations had sediment concentrations significantly greater than the upstream sites (wet wt. means 1855 ug/kg, 892 ug/kg, 238 ug/kg). The average fish whole body PFOA concentration for the two upstream locations was 11.7 ug/kg (wet wt.), while that for the five downstream locations was 106.4 ug/kg. The average PFOA concentration in clams at the two upstream locations was 4.38 ug/kg, while the average for the five downstream locations was 8.42 ug/kg.

Based on available data, APFO does not appear to bioaccumulate in fish. In a study of fathead minnows, the calculated BCF for APFO was 1.8.

Several species were tested to assess the acute toxicity of APFO; these included the fathead minnow (*Pimephales promelas*), bluegill sunfish (*Lepomis machrochirus*), water flea (*Daphnia magna*), and a green algae (*Selenastrum capricornutum*). Comparisons of the different studies are problematic for several reasons. The studies were conducted with different test substances. Generally the ammonium salt or the tetrabutylammonium salt was tested. Purity of the test material is a major concern and was not sufficiently characterized in these tests. In some tests it appeared that 100% test chemical was used, for others a chemical of lesser purity (approximately 27 to 85%) was used. Water, a solvent (isopropanol) or a combination of both was used in other tests, for no obvious stated reason. Finally, only nominal test chemical concentrations were reported; the actual concentrations were not reported.

Twelve tests were conducted with fathead minnows; 96-h LC50 values (based on mortality) ranged from 70 to 843 mg/L. It is unclear why this range is so wide. Assuming these studies are valid, and due to the limitations discussed above, these toxicity values indicate low toxicity. The two acute values for bluegill sunfish also indicate low toxicity (96-h LC50s of >420, and 569 mg/L).

Nine acute tests were conducted with daphnids and 48-h EC50 values (based on immobilization) ranged from 39 to >1000 mg/L. The lower values are indicative of moderate toxicity, but the wide range makes interpretation difficult.

Seven tests were conducted with green algae; 96-h EC50 values (based on growth rate, cell density, cell counts, and dry weights) ranged from 1.2 to >666 mg/L (the Er50 cell density value of 1,000 mg/L is excluded from this discussion). The lower value indicates high to moderate toxicity, based on the acute criteria. The lower value would also be indicative of moderate toxicity, based on the chronic moderate criterion ($.0.1 \leq 10$ mg/L). A 14-d EC50 value of 43 mg/L, based on cell counts, for green algae was also calculated in one study. This is indicative of low chronic toxicity, based on the chronic criterion (10 mg/L). Green algae appeared to be the most sensitive test species in the 44% APFO test sample, daphnids were the next most sensitive, and fathead minnows were the least sensitive.

Human Health Effects and Biomonitoring

Little information is available concerning the pharmacokinetics of APFO in humans. A preliminary study of retired workers suggests simply that the serum half-life is between 1 and 3.5 years. These data provide evidence of the potential to bioaccumulate PFOA in humans. In addition, this study provides preliminary evidence that the serum half-life may be longer in females than in males.

Animal studies have shown that APFO is well absorbed following oral and inhalation exposure, and to a lesser extent following dermal exposure. In rats and dogs, there are major gender differences in the distribution and elimination of APFO. APFO distributes primarily to the liver,

plasma, and kidney, and to a lesser extent, other tissues of the body including the testis and ovary. It does not partition to the lipid fraction or adipose tissue. APFO binds to macromolecules in the tissues listed above. APFO is not metabolized and there is evidence of enterohepatic circulation of the compound. The urine is the major route of excretion of APFO in the female rat, while the urine and feces are both major routes of excretion of APFO in male rats. In female rats, the half-life is 24 h in the serum and 60 h in the liver; in male rats, the half-life is 105 h in the serum and 210 h in the liver. In beagle dogs, the plasma half-life is 254 h in females and 507 h in males. In rats, the elimination half-life is one day in females and 15 days in males. Female rats appear to have a secretory mechanism that rapidly eliminates APFO; this secretory mechanism is either lacking or relatively inactive in males. Other studies in rats have shown that testosterone exerts an inhibitory effect on renal excretion of APFO. Hormonal changes during pregnancy do not appear to change the rate of elimination in rats. The gender difference observed in rats and dogs has not been observed in primates and humans.

There are limited data on PFOA serum levels in workers and the general population. Occupational data from plants in the U.S. and Belgium that manufacture or use PFOA indicate that mean serum levels in workers range from 0.84 to 6.4 ppm. The highest level reported in a worker in 1997 was 81.3 ppm. In non-occupational populations, serum PFOA levels were much lower. In both pooled blood bank samples and in individual samples in both adults and children, mean PFOA levels ranged from 3 to 17 ppb. The highest serum PFOA level reported was in a sample from a child (56 ppb).

Epidemiological studies on the effects of PFOA in humans have been conducted on workers. Two mortality studies, as well as studies examining effects on the liver, pancreas, endocrine system, and lipid metabolism, have been conducted to date. In addition, a morbidity study was also recently submitted.

A retrospective cohort mortality study demonstrated a weak association with PFOA exposure and prostate cancer. A statistically significant association was observed in prostate cancer mortality as length of employment increased. This result was not observed in a recent update to the study; however, the results cannot be directly compared because the exposure categories were modified in the update. In a morbidity study, workers with the highest PFOA exposures for the longest durations sought care more often for prostate cancer treatment than workers with lower exposures.

Another study reported an increase in estradiol levels in workers with the highest PFOA serum levels; however, none of the other hormone levels analyzed indicated any adverse effects. Some of the same employees who participated in the hormone study also were included in a study of cholecystokinin (CCK) levels in employees. No positive association was noted between CCK values and PFOA. The other available study examined cholesterol and other serum components in workers. There did not appear to be any significant differences among workers of different exposure levels, except among obese workers (aspartate amino transferase and alanine amino transferase). However, PFOA was not measured directly, but indirectly as total serum fluorine.

There are many limitations to these studies, but most notably the small number of workers with PFOA serum levels greater than 10 ppm. Therefore, all of these results must be interpreted carefully.

In acute toxicity studies in animals, the oral LD50 values for CD rats were >500 mg/kg for males and 250-500 mg/kg for females, and <1000 mg/kg for male and female Wistar rats. There was no mortality following inhalation exposure of 18.6 mg/L for one hour in rats. The dermal LD50 in rabbits was determined to be greater than 2000 mg/kg. APFO is a primary ocular irritant in rabbits, while the data regarding potential skin irritancy are conflicting.

APFO is not mutagenic. APFO did not induce mutation in either S. typhimurium or E. coli when tested either with or without mammalian activation. APFO did not induce chromosomal aberrations *in vitro* in human lymphocytes when tested with and without metabolic activation up to cytotoxic concentrations. APFO was tested twice for its ability to induce chromosomal aberrations in CHO cells *in vitro*. In the first assay, APFO induced both chromosomal aberrations and polyploidy in both the presence and absence of metabolic activation. In the second assay, no significant increases in chromosomal aberrations were observed without activation. However, when tested with metabolic activation, APFO induced significant increases in chromosomal aberrations and in polyploidy. APFO was negative in a cell transformation assay in C_3H $10T_{½}$ mouse embryo fibroblasts and in the *in vivo* mouse micronucleus assay.

Subchronic studies in rats and mice with 28 and 90-days of exposure have demonstrated that the liver is the primary target organ and that males are far more sensitive than females. Dietary exposure to APFO for 90 days resulted in significant increases in liver weight and hepatocellular hypertrophy in female rats at 1000 ppm (76.5 mg/kg/day) and in male rats at doses as low as 100 ppm (5 mg/kg/day). Analyses of serum and liver levels of APFO showed a marked gender difference that accounts for the difference in sensitivity. In a 90-day study with rhesus monkeys, exposure to doses of 30 mg/kg/day or higher resulted in death, lipid depletion in the adrenals, hypocellularity of the bone marrow, and moderate atrophy of the lymphoid follicles in the spleen and lymph nodes. Unlike rodent studies, analyses of the serum and liver levels did not reveal a gender difference in monkeys, but the sample size was very small (N=2). Chronic dietary exposure of rats to 300 ppm APFO (14.2 and 16.1 mg/kg/day for males and females, respectively) for 2 years resulted in increased liver and kidney weights, hematological effects and liver lesions in males and females. In addition, testicular masses were observed in males at 300 ppm and ovarian tubular hyperplasia was observed in females after exposure to 30 ppm (1.6 mg/kg/day), the lowest dose tested.

Prenatal developmental toxicity studies in rats resulted in death and reduced body weight in dams exposed to oral doses of 100 mg/kg/day or by inhalation to 25 mg/m^3 APFO. There was no evidence of developmental toxicity after oral exposure to doses as high as 150 mg/kg/day, while inhalation exposure to 25 mg/m^3 resulted in reduced fetal body weights. In a rabbit oral developmental toxicity study there was a significant increase in skeletal variations after exposure

to 50 mg/kg/day APFO. There was no evidence of maternal toxicity at 50 mg/kg/day, the highest dose tested.

A two-generation reproductive toxicity study is currently being conducted. A two-generation reproductive toxicity study of PFOS showed high mortality of F1 pups at doses as low as 1.6 mg/kg/day. The results of the APFO study will be important to determine whether a similar effect is observed.

Carcinogenicity studies in Sprague-Dawley (CD) rats show that APFO is weakly carcinogenic, inducing Leydig cell adenomas in the male rats and mammary fibroadenomas in the females following dietary exposure to 300 ppm for 2 years (equivalent to 14.2 mg/kg/day in males and 16.1 mg/kg/day in females). The compound (at 300 ppm) has also been reported to be carcinogenic toward the liver and pancreas of male CD rats.

The mechanism(s) of APFO tumorigenesis is not clearly understood. Available data indicate that the induction of tumors by APFO is due to a non-genotoxic mechanism, involving activation of receptors and perturbations of the endocrine system. The liver carcinogenicity/toxicity of APFO appear to be related to induction of peroxisome proliferation following binding to the peroxisome proliferation activation receptor α (PPAR α) in the liver. Available data suggest that the induction of Leydig cell tumors (LCT) and mammary gland neoplasms by APFO may be due to hormonal imbalance resulting from activation of the PPARα and induction of the cytochrome P450 enzyme, aromatase. Preliminary data suggest that the pancreatic acinar cell tumors are related to an increase in serum level of the growth factor, cholecystokinin.

As the mechanisms of carcinogenic action of APFO have not been fully elucidated, it is assumed that the tumors induced in rats are relevant to humans. Review of available mechanistic data of other drugs and chemicals that induce LCT in animals has led a workshop panel to conclude that all but two modes of induction of the luteinizing hormone (LH), "dopamine agonism" and "GnRH agonism", are considered to be relevant to humans, and that the possibility of induction of Leydig cell adenoma in humans by specific agents with other modes of action cannot be ruled out despite the rarity of LCT in humans. At present, there is no evidence that the induction of LCT by APFO is via the "dopamine agonism" or "GnRH agonism" mode of action. It is recognized that there are quantitative differences in certain biological parameters between rats and humans. However, the principal cell control mechanisms appear similar, and the difference in carcinogenic response is probably quantitative. As binding to the PPARα appears to be the critical event leading to hormonal imbalance and APFO tumorigenesis, and the level of PPARα in human livers is lower than that in rodent liver, it appears that humans may be less sensitive than rodents in the development of LCT, mammary gland tumors, or liver neoplasms.

1.0 Chemical Identity

Chemical Name: Perfluorooctanoic Acid
Molecular formula: C8 H F15 O2

Structural formula: F-CF2-CF2-CF2-CF2-CF2-CF2-CF2-C(=O)-X,

The free acid and some common derivatives have the following CAS numbers:
The perfluorooctanoate anion does not have a specific CAS number.

Free Acid	(X = OM+; M = H)	[335-67-1]
Ammonium Salt	(X = OM+; M = NH4)	[3825-26-1]
Sodium Salt	(X = OM+; M = Na)	[335-95-5]
Potassium Salt	(X = OM+; M = K)	[2395-00-8]
Silver Salt	(X = OM+; M = Ag)	[335-93-3]
Acid Fluoride	(X = F)	[335-66-0]
Methyl Ester	(X = CH3)	[376-27-2]
Ethyl Ester	(X = CH2-CH3)	[3108-24-5]

Synonyms: 1-Octanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-
PFOA

1.1 Physicochemical Properties

For this report, perfluorooctanoic acid is consistently referred to as PFOA. Most of the toxicology studies have been conducted with the ammonium salt of perfluorooctanoic acid, which will be referred to as APFO in this report. PFOA is a completely fluorinated organic acid. The typical structure has a linear chain of eight carbon atoms produced by the telomerization of tetrafluoroethylene. The physical chemical properties noted below are for the free acid, unless otherwise stated. The data for the free acid, pentadecafluorooctanoic acid [335-67-1], is the most complete. The reported vapor pressure of 10 mm Hg appears high, but is consistent with other perfluorinated compounds with similar boiling points. The free acid is expected to completely dissociate in water.

Determination of the vapor pressure of APFO is problematic. For APFO, the recently reported vapor pressure of < 1 x 10E-5 (3M Environmental Laboratory, 1993) seems too low for a material that sublimes as the ammonium salt. This study measured the water solubility of APFO to be > 10%. It was noted in an earlier study that concentrations of 20 g/L "gelled" (3M

Company, 1979). The partition coefficient was reported in these early studies of 5. Another calculated value, -0.9, might not be accurate due to the method used (Hansch and Leo 1979). The formation of an emulsified layer between the octanol and water surface interface would make determination of log P difficult.

The available physicochemical properties for the PFOA free acid are:

MW: 414 (Beilstein, 1975)
MP: 45 - 50 C (Beilstein, 1975)
BP: 189 - 192 C / 736 mm Hg (Beilstein, 1975)
VP: 10 mm Hg @ 25 C (approx.) (Exfluor MSDS)
Sol. - Water: 3.4 g/L (telomeric [mp = 34 C ref. 0.01 - 0.02 mol/L ~4 - 8 g/L) (MSDS from Merck, Fischer, and Chinameilan Internet sites)
pKa: 2.5 (USEPA AR-226 473)
pH (1g/L): 2.6 (MSDS Merck)

Due to the surface-active properties of PFOA, and the test protocol for the OECD method, PFOA is anticipated to form multiple layers in octanol/water, much like those observed for PFOS. Therefore, an n-octanol/water partition coefficient cannot be determined. Water solubility has been reported for PFOA, but it is unclear whether these values are for a microdispersion of micelles, rather than true solubility. Several reports note that PFOA salts self-associate as micelles at higher concentrations. (Simister, 1992; Calfours, 1985; Edwards, 1997). In aqueous solutions, micelles partition between the air / water interface on the surface.

Decomposition of different salts produces perfluoroheptene (loss of metal fluoride and carbon dioxide). This occurs at 320°C for the sodium salt and at 250-290°C (Beilstein 1975). The ammonium salt sublimes at 130°C (USEPA AR-226 473).

The physicochemical properties of PFOA and its derivatives are summarized in Table 1.

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Table 1. Reported Physicochemical Properties

Compound	CAS REG #	MP	BP	VP	Sol.-H2O	Log P
Rf-C(=O)F	335-64-8		131 C			
Rf-CO2H	335-67-1	55 C	189 C	10 mm Hg	3.4 g/L	
Rf-CO2-NH4+	3825-26-1	130 C	sublimes	1 x 10E-5	20 g/L gels	< 5
Rf-C(=O)OMe	376-27-2		159 C			
pH (1 g free acid /L Water) = 2.6			Free acid pKa is approximately 0.6			
Sodium or Silver salts of PFOA decompose above 250 C to generate perfluoroolefins.						

2.0 Production of PFOA and its Salts

PFOA is commercially manufactured by two major alternative processes: 1) the Simons Electro-Chemical Fluorination (ECF) process or 2) the telomerization process.

In the ECF process, an electric current is passed through a solution of anhydrous hydrogen fluoride and an organic feedstock of octanoic acid or a derivative. The ECF process replaces the carbon-hydrogen bonds on molecules of the organic feedstock with carbon-fluorine bonds, in an identical manner used to make PFOS. Perfluorination occurs when all the carbon-hydrogen bonds are replaced with carbon-fluorine bonds. The ECF process yields between 30-45 percent straight chain (normal) perfluorooctanonyl fluoride (PFOF), along with a variable mixture of byproducts and impurities. The output of the ECF process is not a pure chemical, but instead a mixture of isomers and homologues including higher and lower straight-chain homologues; branched-chain perfluoroalkyl fluorides of various chain lengths; straight-chain, branched, and cyclic perfluroalkanes and ethers; and other byproducts (3M Company, 2000a). After disposal or recovery of some of the byproducts and impurities, the acid fluoride is base hydrolyzed in batch reactors to yield PFOA. The PFOA salts are synthesized by base neutralization of the acid to the salt in a separate reactor (3M Company, 2000b).

In the telomerization process, tetrafluoroethylene is reacted with other fluorine-bearing chemicals to yield fluorinated carboxylic acids. This process yields pure straight-chain acids with an even number of carbon atoms. Distillation can be used to obtain pure components (ECT, 1994). Commercial products manufactured through the telomerization process are generally mixtures of perfluorinated compounds with even carbon numbers (Renner, 2001).

3M Company is the largest manufacturer and importer of PFOA and its salts in the United States. 3M has characterized its manufacture of PFOA and its ammonium and sodium salts in 1997 at less than 500,000 kg per year, and its importation at less than 100,000 kg (3M Company, 2000a). These figures may overstate the total production volume of PFOA since the vast majority of

PFOA is consumed in the manufacture of the ammonium or sodium salts. More precise production volumes of PFOA and the ammonium and sodium salts have been reported to USEPA by 3M, but have been claimed as TSCA confidential business information, preventing disclosure in this report.

Industry participants have characterized 3M as the dominant global producer of PFOA-related chemicals, manufacturing approximately 85 percent or more of total worldwide volumes of the ammonium salt of PFOA (FMG, 2001). USEPA has not located information that would contradict this claim. Current production volume information for manufacturers other than 3M has not been provided by industry, nor is it available in USEPA's Chemical Update System (which contains information on non-polymeric organic chemicals manufactured in the United States or imported in volumes above 4,525 kg). Furthermore, there is no information on the total cumulative production volumes of PFOA since initial commercialization.

Since 1985, USEPA has received a total of approximately 25 notifications for PFOA-related chemicals that were not previously on the TSCA Chemical Inventory. Most of these notifications were from companies other than 3M. In most cases, the notifications qualified for the Low Volume Exemption for new chemicals with a production volume less than 10 metric tons per year.

In terms of on-going production, 3M has not committed publicly to a complete phase-out of PFOA and PFOA-related chemicals as it has for PFOS and PFOS-related chemicals. However, 3M has indicated that it is phasing out certain FLUORAD Brand specialty materials that contain PFOA and its salts such as FC-26, FC-118 and FC-143, FX-1001 and others (3M Company, 2000c).

Aside from the United States, OECD Member countries that reportedly have production capacity include France, Germany, Italy, and Japan. There may also be some production in non-OECD countries such as China. Following are companies that may manufacture PFOA and its salts (3M Company, 2000b; Directory of World Chemical Producers, 1998; Dynax, 2000; Renner, 2001; SEMI, 2001):

OECD

- 3M Company (United States)
- DuPont (United States)
- Exfluor Research Corporation (United States)
- PCR Inc. (United States)
- Atofina (France)
- Ciba Specialty Chemicals (Germany)
- Clariant (Germany)
- Dyneon (Germany)
- Hoechst Aktiengesellschaft (Germany)

- EniChem Synthesis S.p.A. (Italy)
- Miteni S.p.A. (Italy)
- Asahi Glass (Japan)
- Daikin (Japan)
- Dainippon (Japan)
- Tohkem Products Corporation (Japan)

Non-OECD

- Chenguang Research Institute of the Chemical Industry (China)
- Shanhai 3F New Materials Co., Ltd. (China)

2.1 Uses of PFOA and its Salts

PFOA is used mainly as a chemical intermediate, and its salts are used in emulsifier and surfactant applications.

According to 3M, the vast majority of PFOA is consumed to make the ammonium or sodium salts. 3M also uses PFOA as a reactive intermediate in the industrial synthesis of a fluoroacrylic ester. The fluoroacrylic ester is used in an industrial coating application (3M Company, 2000a).

The salts of PFOA have additional uses, mostly in surfactant and emulsifier applications. These include the following:

- Processing aid in the industrial synthesis of fluoropolymers and fluoroelastomers such as polytetrafluoroethylene and polyvinylidene fluoride with a variety of industrial and consumer uses (3M Company, 2000a; DuPont, 2000; Daikin, 2001).

- Post-polymerization processing aids in the stabilization of suspensions of fluoropolymers and fluoroelastomers prior to further industrial processing (3M Company, 2000a).

- Processing aid for factory-applied fluoropolymer coatings on fabrics, metal surfaces, and fabricated or molded parts (3M Company, 2000a).

- Extraction agent in ion-pair reversed-phased liquid chromatography (Petritis, 1999).

Based on the physicochemical properties of the salts of PFOA, they may also have other related surfactant or emulsifier uses as a photographic chemical or in the manufacture of electronic components such as semiconductors. These same properties may lead industry to explore PFOA as a replacement chemical for PFOS in other applications in which PFOA is not currently used.